SUPPLEMENTAL MATERIAL

Supplemental Methods

Data S1. Automated external defibrillator (AED) placement optimization model

The previously developed and validated mathematical optimization model[17] used in the study is described below. Overall, the model aims to maximize the number of covered historical OHCAs given the model inputs and constraints outlined as follows:

- z_i is a binary variable indicating whether cardiac arrest *i* is covered
- x_j is a binary variable indicating whether an AED is placed in location *j*
- a_{ij} is a binary data parameter that indicates whether cardiac arrest *i* can be covered by an AED placement at location *j*. OHCAs that can be covered are defined following the OHCA coverage definition used (e.g. within 100m of an accessible AED), as well as those not already covered by an existing AED.
- N is the number of AEDs that are to be placed
- J is the number of candidate locations to place an AED at
- I is the number of cardiac arrests that can be covered

$$
\begin{aligned}
\text{Maximize} \quad & \sum_{i=1}^{I} z_i \\
\text{Subject to} \quad & \sum_{j=1}^{J} x_j \leq N \\
& z_i \leq \sum_{j=1}^{J} a_{ij} x_j, \text{ for all } i = 1, \dots, I \\
& z_i \in \{0,1\}, \text{ for all } i = 1, \dots, I \\
& x_j \in \{0,1\}, \text{ for all } j = 1, \dots, J
\end{aligned}
$$

Model inputs:

- **Candidate AED locations:** Locations to place an AED at (e.g., locations based on a grid system spanning the setting of use, a set of businesses and public locations of interest in the setting of use, etc.).
- **Existing AED locations:** Locations with an AED already placed in the setting of use that provide coverage to historical OHCAs.
- **Historical OHCAs:** The locations of the historical OHCAs in the setting of use.
- **Model Parameter *N*:** A user-defined parameter indicating the number of AEDs to place in the setting of use.

Model outputs:

- **Selected candidate locations for AED placement:** The *N* candidate locations that comprise/are added to an AED network that maximizes OHCA coverage of historical OHCAs.
- **Covered OHCAs:** The set of historical OHCAs covered by the selected candidate AED locations and existing AED locations.

Data S2. Out-of-hospital cardiac arrest (OHCA) coverage sensitivity analysis

We conducted a sensitivity analysis to examine the stability of the results to the sequence of OHCA events over the study period. To do this, the location of each OHCA that occurred during the study period was randomly permuted, while the date and time of each OHCA event were kept the same as the actual sequence. This allowed for the total number of OHCA events in each time period to be the same in the permuted and actual sequence of OHCAs. For each permutation we assessed the controls and interventions by calculating the OHCA coverage, percent coverage, coverage efficiency, and coverage gain. We performed the sensitivity analysis using 10 permutations and generated 95% confidence intervals (CIs) and mean values for the results. Bystander defibrillation and 30-day survival were also estimated based on these coverage results. The mean values and 95% CIs were calculated for each estimated outcome across the 10 permutations.

Data S3. Prediction model design and selection for patient outcome estimation

Data preprocessing and patient outcomes estimation:

To estimate the increase in bystander defibrillation and 30-day survival due to OHCA coverage, we developed two multivariate logistic regression models. To do so, each model was fit on the historical OHCA coverage values from the real AEDs, and historical OHCA values for the Utstein variables: age, sex, response time, bystander witnessed, and bystander CPR. Missing predictor variable values in the OHCA dataset were imputed using the median of non-missing historical values. An additional predictor variable was added to the data set to indicate which cases had a missing value imputed, as well as the variable for which a value was imputed. OHCAs with missing outcome variables were excluded.

For the estimates of bystander defibrillation and 30-day survival, we used all OHCAs in the study period (January 2008 – December 2016) with no missing outcome variable values to fit the prediction models. For bystander defibrillation, a total of 645 of 653 OHCAs were used to fit the models, of which, 575 OHCAs had no missing predictor values (the remaining 70 OHCAs had at least one imputed predictor value). For 30-day survival, a total of 594 of 653 OHCAs were used to fit the models (551 OHCAs had no missing predictor values; 43 OHCAs had at least one imputed predictor value).

Prediction model discriminant threshold calibration:

The discriminant thresholds for the two models when predicting OHCA outcomes were set to 0.21 for the bystander defibrillation model, and 0.43 for the 30-day survival model such that the percentage of predicted outcomes matched the percentage of historical outcomes. After calibration, the models predicted outcomes within 0.1 percentage points of actual outcomes (Table S1).

Data S4. Spline regression model to assess sensitivity of estimated patient outcomes

Regression model development:

Two spline regressions models were developed to estimate the increase in bystander defibrillation and 30-day survival based on distance of an OHCA to the nearest available AED as a robustness check for the estimates generated using OHCA coverage and the logistic regression models. Following the same methodology used to train the logistic regression models, the spline models were fit using the historical distances of OHCAs to the nearest available real AED (instead of OHCA coverage) as well as the processed Utstein variables. The distances to the nearest AED used to train the models were calculated up to 300 m (route distance). OHCAs more than 300 m away from the nearest available AED were set to have a distance 300 m. A binary predictor variable was also developed and used in the model to indicate which OHCAs were more than 300 m away from an AED.

The number of knots in the final spline models were selected based on a grid search parameter tuning approach, where the knots and locations corresponding to the highest out-of-sample AUC calculated through 10-fold cross validation were selected for use. The grid search process considered models with the number of knots used ranging from two to five, where the knots were located at equally spaced percentiles of the distances to the nearest AEDs (e.g., for three knots, the 25th, 50th, and 75th percentiles were used), as well as with two to five knots located at the 5th and 95th percentiles with any remaining knots spaced equally between those percentiles (e.g., for three knots, the 5th, 50th, and 95th percentiles were used). In summary, a total of eight models were considered during this process.

<u>Estimated patient outcomes:</u>

The final bystander defibrillation spline model had five equally spaced knots spanning the percentiles of the distances to the nearest AED (i.e., knots located at the 16.6th, 33.3rd etc. percentiles of the distances to the nearest AEDs). The 30-day survival spline model had two equally spaced knots located at the 33rd and 66th percentiles of the distances to the nearest AED. The AUCs of the cubic spline regression model for bystander defibrillation and 30-day survival were 0.70 (95% CI: 0.65-0.75) and 0.744 (95% CI: 0.692-0.797), respectively. These were slightly higher compared the logistic regression models using coverage as a predictor variable, which had an AUC of 0.69 (95% CI: 0.64-0.73) and 0.736 (95% CI: 0.668-0.803) for bystander defibrillation and 30-day survival, respectively. The discriminant thresholds for the two spline models set to 0.34 for the bystander defibrillation model, and 0.60 for the 30-day survival model such that the percent of predicted outcomes closely matched the percent of historical outcomes.

The models estimated increases in bystander defibrillation from 16.7% to 18.4% (relative increase of 10.1%; P=0.26) and from 31.4% to 36.8% (relative increase of 17.1%; P<0.001) in 30-day survival from the intervention to the control across all 653 OHCAs. The spline regression models estimated larger relative increases in 30-day survival and smaller relative increases in bystander defibrillation compared to our original logistic regression models. Although the estimates differed, the coverage and spline-based distance models demonstrated the same directional effect that the intervention improved estimated outcomes compared to the control.

Table S1. Predicted bystander defibrillation and 30-day survival outcomes for all OHCAs

	Real AEDs OHCAs, n (%)	
	Actual Outcomes **Jan. 2008 to Dec. 2016** **(n=653)***	**Predicted Outcomes** **Jan. 2008 to Dec. 2016** **(n=653)**
Bystander defibrillation	94 (14.6)	95 (14.5)
30-day survival	192 (32.3)	211 (32.3)

*The number of missing values of the 653 OHCAs: bystander defibrillation is n=8; 30-day survival is n=59.

AED=automated external defibrillator; OHCA=out-of-hospital cardiac arrest.

Table S2. Baseline characteristics the covered OHCAs in the primary analysis and real AEDs in Copenhagen during the study period (January 2008 - December 2016). This table summarizes historical characteristics of the covered OHCAs that were used as inputs to the regression models and does not reflect the increase in estimated patient outcomes or potential change in bystander behavior that stem from AEDs placed in either the guidelines control or optimization intervention. Therefore, the potential increase in the proportion of initial heart rhythm or bystander CPR, for example, that would be expected if an AED was placed in a guideline recommended or optimized location would not be seen in the table.

OHCA characteristics	OHCAs covered by real AED placements Jan. 2008 to Dec. 2016 (n=94)*	OHCAs covered in Control: AEDs at every bystander witnessed OHCA with 24/7 availability Jan. 2008 to Dec. 2016 (n=103)†	OHCAs covered in Intervention: Optimal AED locations with 24/7 availability Jan. 2008 to Dec. 2016 (n=158)‡	P value between characteristics of covered OHCAs in each group§
Median age§, y (IQR)	62 (53 - 69)	65 (55 - 75)	64 (53 - 73)	0.234
Men§	59 (53 - 68)	61 (53 - 71)	61 (51 - 70)	0.497
Women§	69 (59 - 76)	80 (67 - 91)	75 (63 - 82)	0.270
Male sex§, n (%)	70 (78.7)	77 (76.2)	117 (75.5)	0.851
Shockable initial heart rhythm§, n (%)	52 (55.3)	48 (46.6)	73 (46.2)	0.329
Bystander witnessed arrest§, n (%)	71 (77.2)	77 (77.0)	112 (73.2)	0.708
Received bystander CPR§, n (%)	77 (83.7)	77 (77.0)	113 (73.4)	0.175

*Number of missing values for variables available and described in OHCAs covered by Real AEDs: age (n=6), sex (n=5), Bystander witnessed arrest (n=2), Received bystander CPR (n=2).
†Number of missing values for variables available and described in OHCAs covered in Control: age (n=5), sex (n=2), Bystander witnessed arrest (n=3), Received bystander CPR (n=3).
‡Number of missing values for variables available and described in OHCAs covered in Intervention: age (n=8), sex (n=3), Bystander witnessed arrest (n=5), Received bystander CPR (n=4).
§No significant differences were found between the characteristics of OHCAs covered by real AED placements, the control, and intervention based on one-way ANOVA (for age characteristics) and chi-squared (for gender, initial heart rhythm, bystander witnessed and bystander CPR characteristics) tests.

CPR=cardiopulmonary resuscitation; OHCA=out-of-hospital cardiac arrest.

Table S3. Robustness of OHCA coverage and percent coverage in the control placement strategy sensitivity analysis when permuting the order of OHCA incidents

Number of AEDs placed in final network, N		131
Control	OHCA coverage, n (95% CI)	30.0 (28.5-31.5)
	OHCA coverage, % (95% CI)	4.6 (4.4-4.8)
	Number of AEDs per covered OHCA	4.4 (4.2-4.6)
Intervention	OHCA coverage, n (95% CI)	65.2 (59.7-70.7)
	OHCA coverage, % (95% CI)	10.0 (9.1-10.8)
	Number of AEDs per covered OHCA	2.1 (1.9-2.2)
Coverage gain of intervention over control, %		118.2 (100.0-136.5)

AED=automated external defibrillator; OHCA=out-of-hospital cardiac arrest.

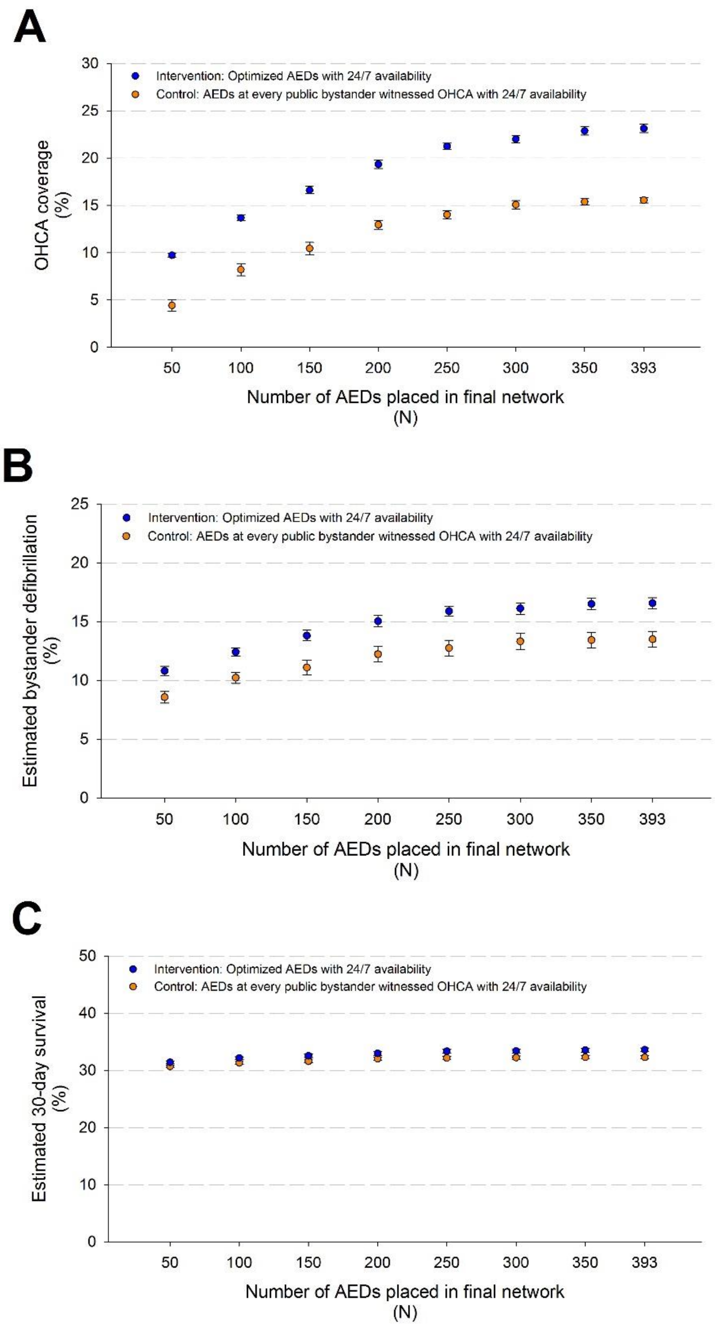
Table S4. Baseline characteristics the covered OHCAs in the sensitivity analysis and real AEDs in Copenhagen during the study period (January 2008 - December 2016). This table summarizes historical characteristics of the covered OHCAs that were used as inputs to the regression models and does not reflect the increase in estimated patient outcomes or potential change in bystander behavior that stem from AEDs placed in either the guidelines control or optimization intervention. Therefore, the potential increase in the proportion of initial heart rhythm or bystander CPR, for example, that would be expected if an AED was placed in a guideline recommended or optimized location would not be seen in the table.

OHCA characteristics	OHCAs covered by real AED placements Jan. 2008 to Dec. 2016 (n=94)*	OHCAs covered in Control: AEDs at hotspots of 2 bystander witnessed OHCAs with 24/7 availability Jan. 2008 to Dec. 2016 (n=33)†	OHCAs covered in Intervention: Optimal AED locations with 24/7 availability Jan. 2008 to Dec. 2016 (n=60)‡	P value between characteristics of covered OHCAs in each group§
Median age§, y (IQR)	62 (53 - 69)	70 (60 - 77)	62 (52 - 73)	**0.037**
Men§	59 (53 - 68)	67 (56 - 71)	60 (53 - 71)	0.339
Women§	69 (59 - 76)	81 (80 - 84)	73 (44 - 80)	**0.033**
Male sex§, n (%)	70 (78.7)	25 (75.8)	45 (77.6)	0.942
Shockable initial heart rhythm§, n (%)	52 (55.3)	14 (42.4)	26 (43.3)	0.242
Bystander witnessed arrest§, n (%)	71 (77.2)	26 (78.8)	41 (69.5)	0.487
Received bystander CPR§, n (%)	77 (83.7)	31 (93.9)	46 (78.0)	0.138

*Number of missing values for variables available and described in OHCAs covered by Real AEDs: age (n=6), sex (n=5), Bystander witnessed arrest (n=2), Received bystander CPR (n=2).
†No missing values for variables of the OHCAs covered in Control
‡Number of missing values for variables available and described in OHCAs covered in Intervention: age (n=5), sex (n=2), Bystander witnessed arrest (n=1), Received bystander CPR (n=1).
§Significant differences were identified between the characteristics of OHCAs covered by real AED placements, the control, and intervention based on one-way ANOVA (for age characteristics) and chi-squared (for gender, initial heart rhythm, bystander witnessed and bystander CPR characteristics) tests.

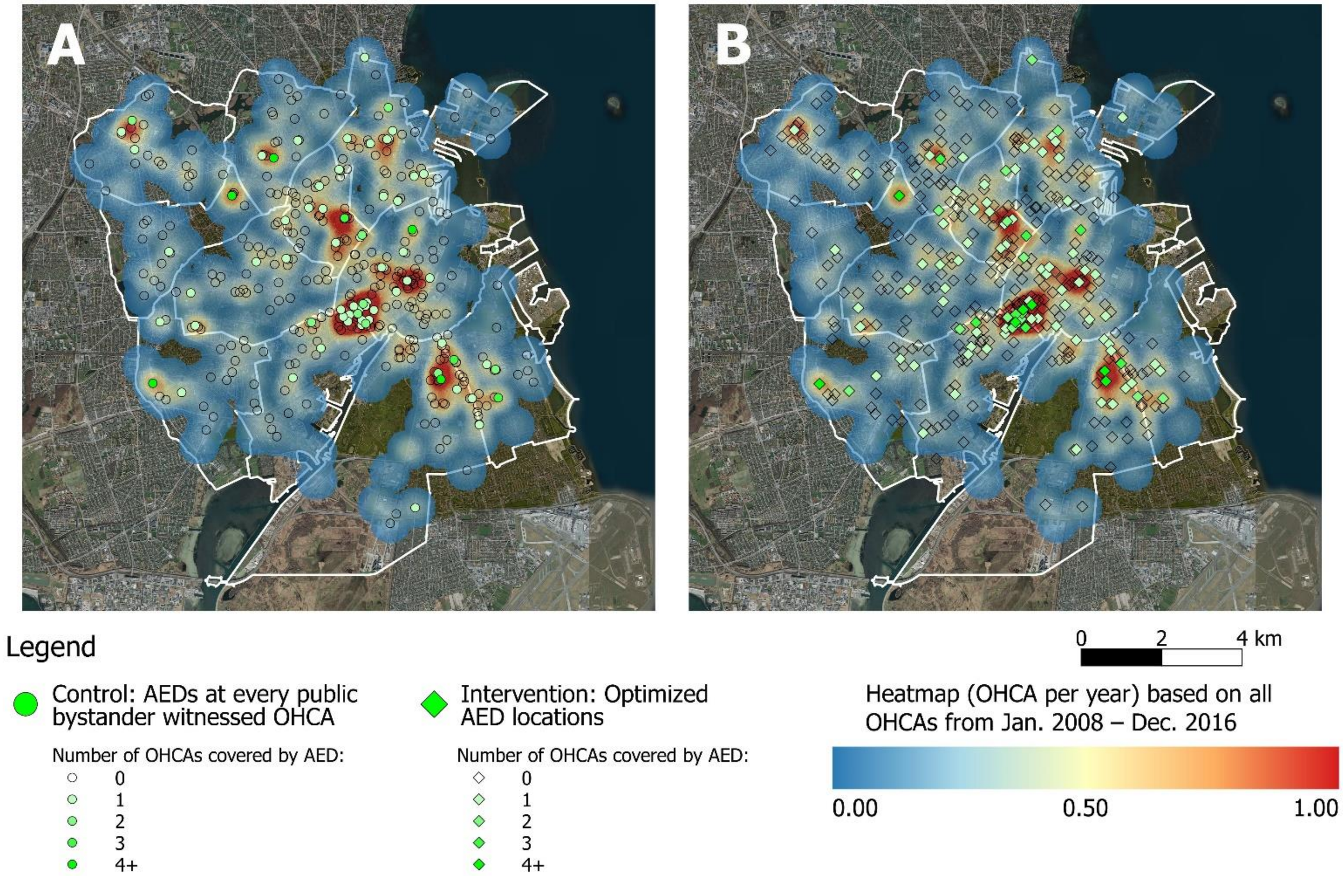
CPR=cardiopulmonary resuscitation; OHCA=out-of-hospital cardiac arrest.

Figure S1. Robustness of OHCA coverage (A), estimated bystander defibrillation (B), and estimated 30-day survival (C) over the 653 OHCAs during the study period for networks with between 50 and 393 AEDs when permuting the order of OHCA incidents.



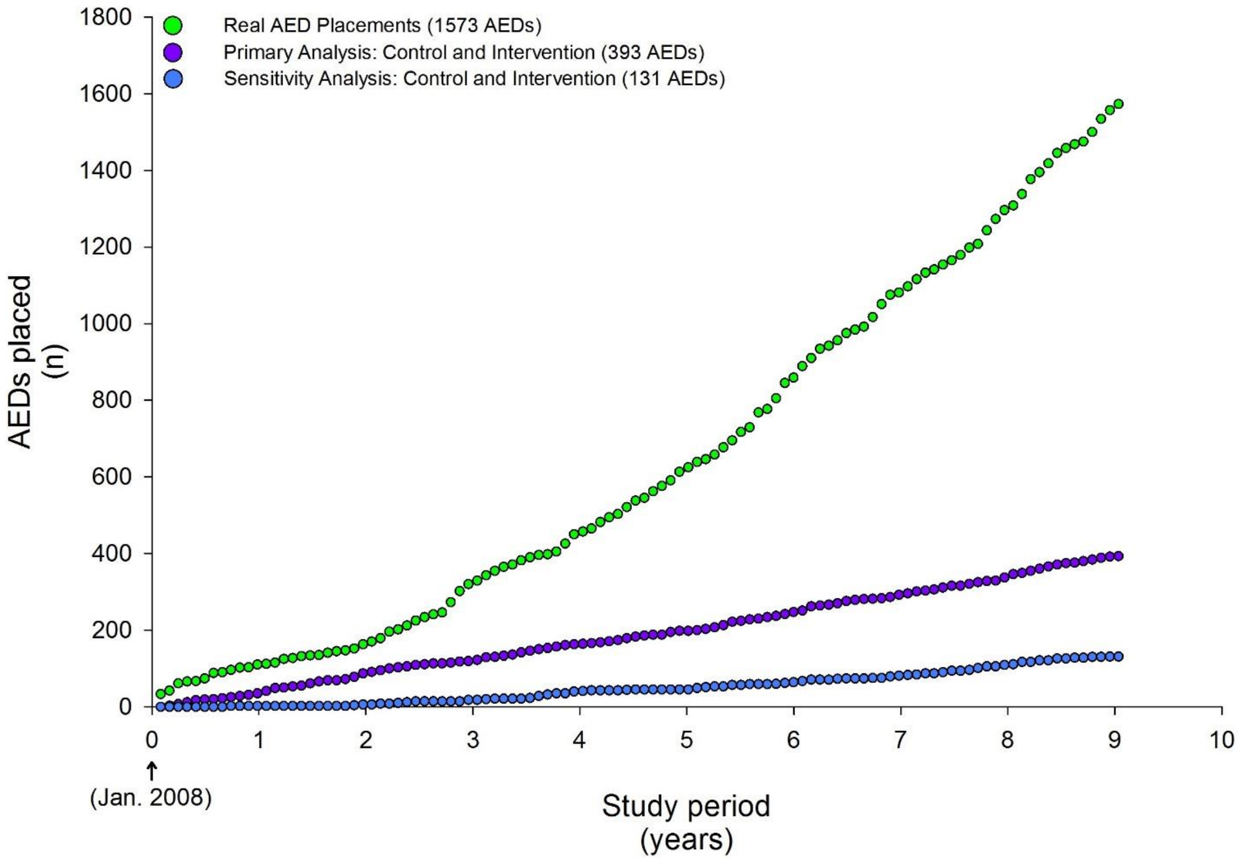
The mean and corresponding 95% confidence intervals of the three outcomes over the 10 permutations are shown for the control and intervention. AED=automated external defibrillator; OHCA=out-of-hospital cardiac arrest.

Figure S2. A visualization of the 393 AED placements in control (A) and intervention (B) at the end of the study period.



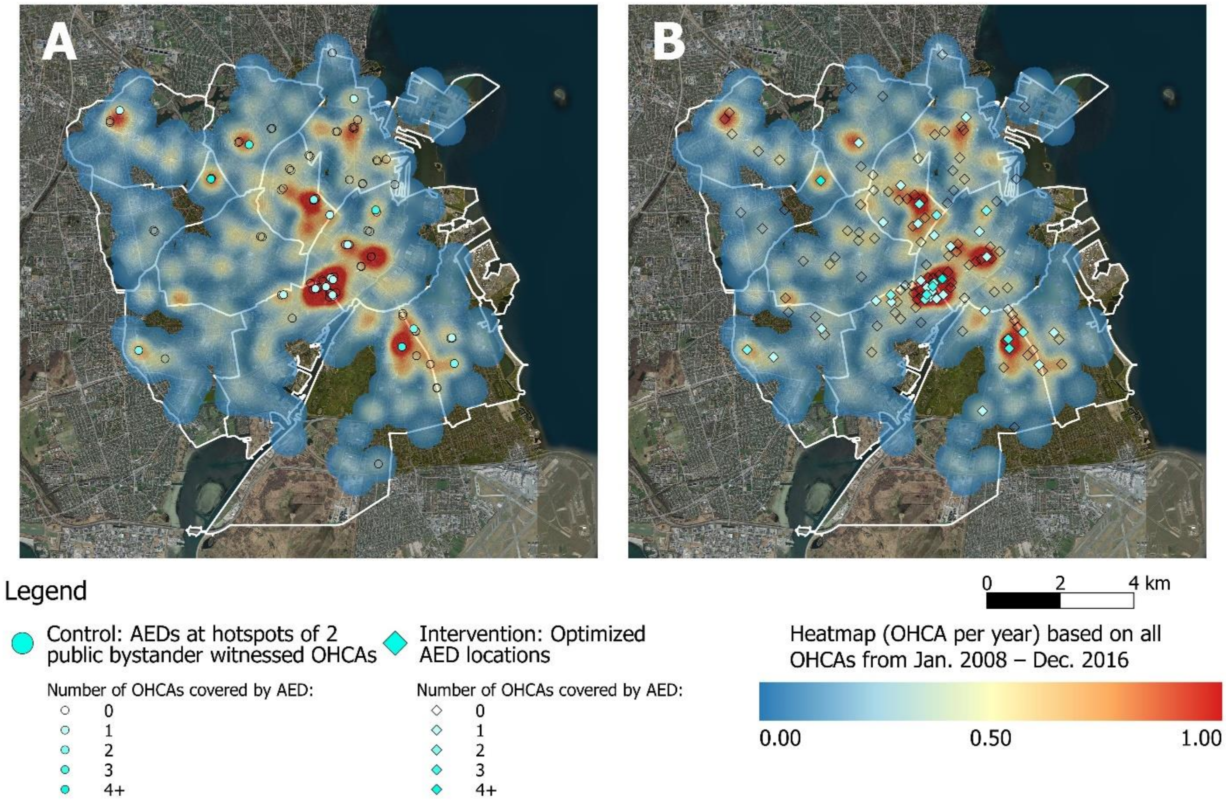
The number of OHCAs covered for each AED is shown as a green gradient ranging from zero to four or more covered OHCAs. The AEDs placements are overlaid on a heat map of all OHCAs that occurred during the study period (Jan. 2008 – Dec. 2016). AED=automated external defibrillator; OHCA=out-of-hospital cardiac arrest.

Figure S3. The number of AEDs placed over the study period for the optimization approach (intervention), guidelines-based approach (control) in the primary analysis and sensitivity analysis, as well as for the real AED placements.



AED=automated external defibrillator; OHCA=out-of-hospital cardiac arrest.

Figure S4. A visualization of the 131 AED placements in the control (A) and intervention (B) in the sensitivity analysis at the end of the study period.



The number of OHCAs covered for each AED is shown as a green gradient ranging from zero to four or more covered OHCAs. The AEDs placements overlay a heatmap of all OHCAs that occurred during the study period (Jan. 2008 – Dec. 2016). AED=automated external defibrillator; OHCA=out-of-hospital cardiac arrest.